REMARKS

I. Status of Claims

Claims 4, 6, 8, 10, 12, 14-19, 22-26, and 28 are pending in this application. Claims 16-19, 22-25, and 28 are withdrawn. Claims 4, 6, 8, 10, 12 and 14 have been amended. Claims 1-3, 5, 7, 9, 11, 13, 20-21, 27, and 29-31 are canceled. The amendment introduces no new subject matter.

II. Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 4-14 and 26 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants respectfully traverse the rejection and its supporting remarks.

Applicants have amended the claims to the five proteins and variants of the five proteins. The specification on page 2, line 24 through page 6, line 20, provides a good summary these five antigens. By way of example as indicated on page 2, line 25 through page 3, line 18, NadA has been described including alignments showing conserved regions, expression of variants and fragments have been explored, etc. Furthermore, many allelic variants of NMB1870 (741) have been disclosed. The specification cites to two sources on page 3, lines 30-31, one of which provides 22 sequences and the other of which disclosed 23 sequences.

Thus, the present invention is directed to combinations of known polypeptides and variants of such polypeptides much like *Capon* referred to in the MPEP which was a combination of two known proteins. More on point is *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006), summarized in the MPEP in section 2163(a)(1). The claim at issue in *Falkner* was:

> Claim 1 A vaccine comprising (a) a defective poxvirus that lacks a function imparted by an essential region of its parental poxvirus, wherein (i) said defective poxvirus comprises a DNA polynucleotide encoding an antigen and said DNA polynucleotide is under transcriptional control of a promoter, and (ii) the function can be complemented by a complementing source; and (b) a pharmaceutically acceptable carrier.

The Federal Circuit upheld this claim as enabled and meeting the written description requirement despite the fact that the specification did not disclose a single working embodiment within the scope or the sequence of any poxvirus. This claim appears to cover all possible poxviruses including all known and sequenced species as well as all species that are unknown. By way of example, the vaccinia virus is a poxvirus with a genome of 190 kb which encodes 250 genes. The number of permutations of this genome alone which would fall under the scope of claim 1 is far, far greater than the scope that the Examiner calculated for the previously pending claims for this application, so clearly merely calculating a very large number is not sufficient for establishing that the written description has not been met given that the Federal Circuit found the claims of *Faulkner* met the written description requirement. In this case, the applicants have demonstrated that the five antigens combined actually work together and provide protection across a wide range of *N. meningitidis* serogroup B strains. One of skill in the art would infer that these antigens must have epitopes that are in common across a significant fraction of strains. Thus, one of skill in the art would accept that the variants of the proteins that were isolated from other *N. meningitidis* serogroup B strains, including those disclosed in the specification, should have the same epitopes as found in the proteins tested and therefore should be capable of providing the claimed protection. Therefore, one of skill in the art would accept that the applicant had possession of the presently claimed invention. By way of comparison to *Falkner*, the presently pending claims are directed to five proteins and variants thereof from a single serogroup of a single species of bacteria *N. meningitis* serogroup B whereas *Faulkner* was covering an entire family of viruses including at least one that has 250 genes. Applicants have provided a number of variants of each of the protein in the specification and references to additional variants whereas *Faulkner* did not provide a single example of a variant that worked. The fact that the present claims may cover variants that could be obtained from *N. meningitis* serogroup B that have not been sequenced cannot be a bar to meeting the written description requirement as *Faulkner* covered all poxviruses which must include many whole strains of poxvirus that have not been sequenced (by way of example, the Wikipedia page on Poxviridae currently lists two entire subfamilies with a total of eleven genera. Therefore, if one of skill in the art would recognize that the inventors of *Faulkner* were in possession of that invention, one of skill in the art would clearly understand that the inventors were in possession of the presently pending claims.

Applicants respectfully request that the Examiner withdraw the rejection of claims 4-14 and 26 under 35 U.S.C. § 112, first paragraph, written description.

III. Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 4-14 and 26 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to enable the claims to their full scope.

Applicants respectfully traverse the rejection and its supporting remarks. Applicants respectfully traverse the rejection and its supporting remarks. Applicants have amended the claims to cover the cited proteins and variants thereof. One of skill in the art would have no difficulty making and using compositions within the scope of the claims. As discussed above, one of skill in the art would infer that these antigens must have epitopes that are in common across a significant fraction of strains. Thus, one of skill in the art would accept that the variants isolated from other *N. meningitidis* serogroup B strains (including at a minimum those strains against which the tested composition provided protection), including those disclosed in the specification, should have those epitopes and therefore should be capable of providing the claimed protection. Furthermore, as the claims to *Faulkner* covered poxviruses that are as yet unsequenced, it should not matter that the presently pending claims cover variants of the cited proteins that could be obtained from *N. meningitidis* serogroup B strains for which the claimed proteins have not been sequenced. The disclosed proteins would allow one of skill in the art to readily recognize newly sequenced proteins from other *N. meningitidis* serogroup B strains and one of skill in the art would appreciate that cloning and sequence these proteins from new *N. meningitidis* serogroup B strains would be a trivial matter. Similarly, it is reasonable to assume that the Federal Circuit affirmed that the claims of *Faulkner* were enabled despite covering poxvirus species that have yet to be identified due to the species that had been sequenced to date based upon a similar reasoning that it would be easy to identify newly sequenced poxviruses as being poxviruses given the sequences to date.

Applicants respectfully request that the Examiner withdraw the rejection of claims 4-14 and 26 under 35 U.S.C. § 112, first paragraph, enablement.

IV. Rejection under 35 U.S.C. § 103(a)

Claims 4-14 and 26 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Fraser *et al.* (WO 99/57280, 1999) in view of Commanducci *et al.* (J. Exp. Med., 195:1445-1454, 6/2002).

Applicants respectfully traverse the rejection and its supporting remarks.

No prima facie case of obviousness

The Examiner has asserted that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the same purpose, citing to *In re Kerkhoven*. The Examiner similarly cites to *KSR International Co. v. Teleflex Inc.*, No. 04-1350 (U.S. Apr. 30, 2007) for what is the same proposition, i.e., combining known elements that predictably yield a known result is obvious. However, antigens cannot be combined to predictably to improve the composition. Thus, neither *In re Kerkhoven* nor *KSR* are relevant to this situation as both cases were dealing with simple technologies – brakes in *KSR* and detergent additives in *In re Kerkhoven* – that can be predictably combined. Even with the superior antigens identified by the inventors in the instant specification, the results are clearly not additive. Page 33 shows the results of testing the three polypeptides alone or in combination against specific strains of *N. meningitidis* serogroup B. In certain instances such as against 394/98, the antigens are able to combine synergistically rather than additively. In other cases such as against C11, the combinations of the antigens produce less than an additive immune response. Taken in isolation, if one wanted a vaccine against just strain C11 using just the third polypeptide without the other two would produce the highest immune response. Thus, it is not predictable whether antigens can be combined to produce a better result that the two antigens used alone. At best, it may be obvious to try all possible combinations of antigenic proteins for *N. meningitidis* serogroup B to determine which can be used together to improve the results obtained.

Furthermore, the Examiner has incorrectly asserted that the vaccine tested by Guiliani is not covered by the currently pending claims. First, the independent claim 4 is not limited to separate polypeptides. The Examiner required election between claim 1-14 which included two or more

polypeptides and claim 15 wherein two or more of the polypeptides are linked and the applicants elected the claims to two or more polypeptides, but claim 4 is a generic linking claim as evidenced by the fact that withdrawn species claim 15 depends from claim 4 and always has as of the original filing. Thus, while Guiliani may represent a non-elected species of the generic linking claim of claim 4, the composition is still within the scope of claim 4. Furthermore, the five antigens of Guiliani are the same as the five presently claimed. Pending claim 4 covers "(1) a 'NadA' protein or variant thereof; (2) a 'NMB1870' protein or variant thereof; (3) a 'NMB2091' protein or variant thereof; (4) a 'NMB1030' protein or variant thereof; and (5) a 'NMB2132' protein or variant thereof," while as indicated on page 10835, table 1, Guiliani used GNA2132, GNA1030, GNA2091, GNA1870, and NadA. NMB merely stands for "*N. Meningitidis* serogroup B" as sequenced and number by Tattelin *et al.*, while GNA stands for "Genome derived Neisserial Antigen" which numbering is based upon the *N. Meningitidis* serogroup B genome as sequenced and numbered by Tattelin *et al.* GNA#### and NMB#### as applicants understand it are used interchangeably in the art. Thus the antigens used by Guiliani are within the scope of the presently pending claims.

Finally, as discussed in the prior response, the Examiner has engaged in pure hindsight reconstruction. Fraser *et al.* disclose more than 1500 polypeptides from three *Neisserial* bacteria. The Examiner has asserted that it would be obvious to one of skill in the art to select the five currently claimed polypeptides from that set of 1500 polypeptides when there are more than 7,543,243,012,536,000 combinations of five polypeptides in Fraser *et al.* (1500 x 1499 x 1498 x 1497 x 1496). The Examiner has cited no reason one of skill in the art would select the claimed combination from over seven quadrillion possible combinations. As discussed above, the Examiner has not provided any support for his assertion that combination of any two random antigens will improve the immunogenicity of the combination. Thus, there is no teaching of the disclosed compositions being useful for the claimed activity, so there would be no reason to select the exact five antigens as claimed.

Secondary considerations – unexpected result

Applicant's thank the Examiner for indicating that he was relying upon the results in the instant specification for the assertion that NadA provides the asserted coverage. Applicants have

amended the present claims to more clearly define the surprising result as providing protection across three of the lineages. Neither of the two cited references teaches that any of the polypeptides disclosed in either when administered to an individual in combination would result in the claimed "antibody response is bactericidal against two or more of hypervirulent lineages A4, ET-5 and lineage 3 of *N. meningitidis* serogroup B." Furthermore, the instant specification does not teach that the individual antigens would provide this coverage. Thus, the claimed invention provides a superior result which rebuts any *prima facie* case of obviousness. As discussed above, this superior and unexpected result is the very result which makes this a practical, real-world vaccine, i.e., it provides broad coverage against a range of hypervirulent strains.

As discussed above, Giuliani *et al.* does disclose results obtained with the presently claimed five antigens in a vaccine composition. The presently claimed invention with MF59 as an adjuvant as indicated in Figure 3 provides dramatic coverage across many strains. Even with alum as an adjuvant, the vaccine provides one hundred percent coverage across ET5 and A4 which is commensurate in scope as claimed. This is an unprecedented result. This application and the Giuliani *et al.* paper are in fact the first demonstration of reverse vaccinology pioneered by the inventor Rino Rappuoli, screening a genome for likely antigens and then carefully narrowing the list of candidates to that subset that when combined can provide this kind of broad coverage across *N. meningitidis* serogroup B. See *PNAS*, 103(29):10831-10833 (2006), submitted previously. As discussed above, one of skill in the art would infer that these antigens must have epitopes that are in common across a significant fraction of strains. Thus, one of skill in the art would accept that the variants of the proteins that were isolated from other *N. meningitidis* serogroup B strains, including those disclosed in the specification, should have the same epitopes as found in the proteins tested and therefore should be capable of providing the surprising result.

Applicants respectfully request that the Examiner withdraw the rejection of claims 4-14 and 26 under 35 U.S.C. § 103(a).

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002100300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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